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(54) Title: METHODS OF TREATMENT USING A GASTRIC RETAINED GABAPENTIN DOSAGE

(57) Abstract: A method of treatment for epilepsy and other disease states is described, which comprises the delivery of gabapentin in a gastric retained dosage form.

METHODS OF TREATMENT USING A GASTRIC RETAINED GABAPENTIN DOSAGE

Background Of The Invention

Technical Field

The present invention relates to the use of gabapentin in a gastric retained dosage form. More specifically, the invention relates to the use of such dosage form to treat epilepsy and other disease states.

Background

Gabapentin (1-(aminomethyl)cyclohexaneacetic acid) is an anti-epileptic drug that is currently available in 100 mg, 300 mg and 400 mg hard shell capsule as well as 600 mg and 800 mg tablet dosage forms, with recommended dosing of 900 mg to 1800 mg total daily dose in three divided dosages. The oral bioavailability is dose-dependent, with approximately 60% bioavailability for a dose in the range of 300-400 mg, but with only 35% bioavailability for a dose of 1600 mg (Bourgeois, *Epilepsia* 36 (Suppl. 5):S1-S7 (1995); Gram, *Epilepsia* 37 (Suppl. 6):S12-S16 (1996)). The decrease in bioavailability with dose has been attributed to carrier-mediated absorption (Stewart, et al., *Pharmaceutical Research* 10(2):276-281 (1993).

In early work with rats, Vollmer, et al., *Arzneim-Forsch/Drug Research* 36(I, Nr. 5):781-892 (1986) found that the absorption site for gabapentin was the duodenum. The absorption of gabapentin occurs relatively slowly with the peak plasma concentration occurring approximately 2-6 hours after dosing (Bourgeois, *supra*). The elimination of gabapentin is exclusively through renal pathways (Chadwick; *The Lancet* 343:89-91 (1994); Vollmer, *supra*; Thomson, et al., *Clin. Pharmacokinet.* 23(3):216-230 (1992); and Riva, et al., *Clin. Pharmacokinet.* 31(6):470-493 (1996)) with reported half-lives of 5-7 hours (Chadwick, *supra*) and 6-7 hours (Gram, *supra*).

A once- or twice-daily dosage form of gabapentin would be expected to improve compliance and therefore a controlled release dosage form has some distinct advantages over the conventional immediate release formulations. In addition, a controlled release dosage form would lower the maximum plasma concentration, and this may result in reduced side effects. Since gabapentin is absorbed high in the gastrointestinal tract, by

means of a saturable transport mechanism, a gastric retained dosage form is particularly beneficial for delivery of gabapentin since the dosage form would be able to keep the drug in the region of absorption and show improved bioavailability by virtue of the slower release rate that avoids saturation of the carrier mediated transport of conventional dosages.

Summary Of The Invention

One aspect of the invention relates to a method of treating epilepsy comprising administering a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.

Yet another aspect of the invention relates to a method of treating neuropathic pain comprising administering a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.

Still another aspect of the invention relates to an improved method of administering a therapeutically effective amount of gabapentin to a patient in need thereof, the improvement comprising administering gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form.

Description Of The Invention

The invention relates to a method of treating a disease state, such as epilepsy, by administering gabapentin in a once- or twice-daily gastric retained dosage form. The gastric retained dosage form is particularly beneficial for delivery of gabapentin due to its prolonged transit in the upper gastrointestinal tract, which allows the drug to be absorbed adequately in the preferred region of absorption. In addition, a gastric retained dosage form increases the t_{max} and allows for a smoother, more prolonged anti-spasmolytic effect. This dosage form also lowers the C_{max} and may result in reduced incidence and/or severity of CNS side effects of the drug, such as somnolence, ataxia, fatigue and dizziness.

Method of Treatment

The instant invention is a method of treating a disease state comprising administering a therapeutically effective amount of gabapentin, or a pharmaceutically

acceptable salt thereof, once- or twice-daily in a gastric retained dosage form to a mammal in need of such treatment. As used herein, the term "treating" covers treating the specified disease in a mammal, particularly a human, and includes:

(i) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it;

(ii) inhibiting the disease, i.e. arresting its development; or

(iii) relieving the disease, i.e. causing regression of the disease.

One embodiment of the invention relates to an improved method of administering a therapeutically effective amount of gabapentin to a patient in need thereof, the improvement comprising administering gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form.

Other embodiments of the invention relate to methods of treating specific disease states comprising administering a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment. Such methods find utility in treating numerous disease states that are currently being treated with conventional immediate release formulations of gabapentin and include, by way of illustration and not limitation, epilepsy; neuropathic pain; psychiatric disorders such as bipolar disorder and panic disorder; movement disorders such as restless leg syndrome, periodic movement disorder of sleep, essential tremor and acquired nystagmus; and prophylaxis of migraine headaches.

The invention also contemplates administering one or more additional therapeutic agents with the gabapentin treatment. The selection of these additional therapeutic agents will depend upon the specific disease state being treated, and are described in detail below.

Active Ingredient

The active ingredient in the method of the invention is gabapentin. Gabapentin is preferably used in the free amphoteric form. Pharmaceutically acceptable salt forms that retain the biological effectiveness and properties of gabapentin and are not biologically or otherwise undesirable can also be used and may show superior bioavailability. As used herein, the term "gabapentin" is intended to include the agent itself, as well as its pharmaceutically acceptable salts.

Pharmaceutically acceptable salts may be amphoteric and may be present in the form of internal salts. Gabapentin may form acid addition salts and salts with bases. Exemplary acids that can be used to form such salts include, by way of example and not limitation, mineral acids such as hydrochloric, hydrobromic, sulfuric or phosphoric acid or organic acids such as organic sulfonic acids and organic carboxylic acids. Salts formed with inorganic bases include, for example, the sodium, potassium, lithium, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, for example, the salts of primary, secondary and tertiary amines, substituted amines including naturally-occurring substituted amines, and cyclic amines, including isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethyl aminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, fumarate, maleate, succinate, acetate and oxalate.

Additional Therapeutic Agents

The methods of the invention also contemplate the addition of one or more therapeutic agents with the gabapentin treatment.

For those embodiments of the invention where the gabapentin gastric retained dosage form is administered to treat epilepsy, such additional therapeutic agents can be other anti-epileptics or anticonvulsants, which include, by way of illustration and not limitation, hydantoins, iminostilbenes, valproates, phenyltriazines, barbiturates, deoxybarbiturates, benzodiazepines and carbamates. Such additional agents are preferably hydantoins, iminostilbenes, valproates or phenyltriazines.

The following examples of compounds within each of these classes is intended to be illustrative and not limiting in any manner. Examples of suitable hydantoin anticonvulsants include ethotoin, fosphenytoin, mephenytoin, and, preferably, phenytoin. An examples of a suitable iminostilbene is carbamazepine. Examples of suitable valproates include valprioic acid and sodium valproate. An exemplary suitable phenyltriazine is lamotrigene. A suitable barbiturate is phenobarbital and an exemplary deoxybarbiturate is primidone. An example of a suitable benzodiazepine is clorazepate. A suitable carbamate is felbamate.

For those embodiments of the invention where the gabapentin gastric retained dosage form is administered to treat neuropathic pain, such additional therapeutic agents can

be selected from the group consisting of other anticonvulsants, tricyclic antidepressants, levadopa, and opioids.

The following examples of compounds within each of these classes is intended to be illustrative and not limiting in any manner. Examples of suitable anticonvulsants include carbamazepine, phenytoin and lamotrigine. Suitable tricyclic antidepressants include amitriptyline, imipramine, clomipramine and desipramine. Examples of suitable opioids include oxycodone and tramadol.

For those embodiments of the invention where the gabapentin gastric retained dosage form is administered to treat psychiatric disorders, such additional therapeutic agents can be selected from the group consisting of lithium, carbamazepine, valproate, trifluoperazine, clonazepam, risperidone, lorazepam, venlafaxine, clozapine, olanzapine, benzodiazepines, neuroleptics, tricyclic antidepressants, selective serontin reuptake inhibitor (SSRI's), buprupion, and nefadone.

For those embodiments of the invention where the gabapentin gastric retained dosage form is administered to treat bipolar disorder, such additional therapeutic agents can be selected from the group consisting of lithium, carbamazepine, valproate, trifluoperazine, clonazepam, risperidone, lorazepam, venlafaxine, clozapine, olanzapine, benzodiazepines, and neuroleptics.

For those embodiments of the invention where the gabapentin gastric retained dosage form is administered to treat depression, such additional therapeutic agents can be selected from the group consisting of tri-cyclic anti-depressants, SSRI's, bupropion, venlaxatine, and nefadone.

For those embodiments of the invention where the gabapentin gastric retained dosage form is administered to treat manic disorders, such additional therapeutic agents can be selected from the group consisting of diazepam, and oxazepam.

For those embodiments of the invention where the gabapentin gastric retained dosage form is administered to treat movement disorders, such additional therapeutic agents can be selected from the group consisting of benzodiazepines, dopaminergic agents, and opiates, particularly levodopa/carbidopa and clonazepam.

For those embodiments of the invention where the gabapentin gastric retained dosage form is administered for prophylactic treatment of migraine headaches, such additional therapeutic agents can be selected from the group consisting of tricyclic

antidepressants (amitriptyline, doxepin, imipramine, maprotiline, protriptyline, desipramine), SSRI (fluoxetine), triptine (sumatriptan, etc.), and ergotamine.

Dosage

In general, the term "therapeutically effective amount" refers to that amount which is sufficient to effect treatment, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending on the subject being treated, the severity of the disease state and the manner of administration, and may be determined routinely by one of ordinary skill in the art.

In particular, for use in the treatment of epilepsy or neuropathic pain with a gastric retained dosage form, gabapentin may be used at doses appropriate for treating epilepsy or neuropathic pain with immediate release dosage forms. However, the gastric retained dosage form is designed to provide for bioavailability of gabapentin at a level greater than or equal to 80% (≥80%) relative to an equal dose of an immediate release dosage form. Typically, the method of the invention will involve administering gabapentin on a once- or twice-daily basis for as long as the condition persists.

An effective dosage of gabapentin for the treatment of epilepsy is typically in the range of about 300-3600 mg/day, typically about 900-2400 mg/day, more typically about 900-1800 mg/day.

An effective dosage of gabapentin for the treatment of neuropathic pain is typically in the range of about 100-4800 mg/day, typically about 300-3600 mg/day, more typically about 900-2400 mg/day.

An effective dosage of gabapentin for the treatment of psychiatric disorders is typically in the range of about 100-4800 mg/day, more typically about 900-3600 mg/day.

An effective dosage of gabapentin for the treatment of movement disorders is typically in the range of about 100-4000 mg/day, typically about 200-2700 mg/day, more typically about 500-2700 mg/day.

An effective dosage of gabapentin for the prophylactic treatment of migraine headaches is typically in the range of about 200-4000 mg/day, typically about 500-3600 mg/day, more typically about 900-2400 mg/day.

Dosage Regimen

The methods of the invention provide a once- or twice-daily dose of the gabapentin gastric retained dosage form. The dosage can be administered at any time, but it is preferred that the dosage is administered at the same approximate time each day and in approximately 12 hour intervals for the duration of treatment. In addition, it is preferred that the gastric retained dosage form be taken with food, for example with the morning or evening meals.

Accordingly, in one embodiment of the invention, gabapentin is administered once-daily, for example, in the morning (e.g., upon rising or with the morning meal) or in the evening (e.g., with the evening meal or near bedtime).

In another embodiment of the invention, gabapentin is administered twice-daily, for example, with the first dose being in the morning (e.g., upon rising or with the morning meal) and the second dose being in the evening (e.g., with the evening meal or near bedtime).

In another aspect of the invention, the method of administering a therapeutically effective amount of gabapentin in a gastric retained dosage form further includes administering one or more additional therapeutic agents.

The additional therapeutic agents can be administered at the same time or at a different time than the administration of gabapentin, and will depend upon the nature of the disease being treated as well as the agent itself. For example, when the additional agent is another anti-epileptic, a twice-daily dose is sufficient and it may be administered at the same time or at a different time than gabapentin. For purposes of facilitating patient compliance, administration of any of the aforementioned additional agents at the same time is preferred.

Dosage Form

There are several drug delivery systems that are suitable for use in delivering gabapentin in the method of the invention as they are particularly tailored to be gastric-retained dosages, such as the swellable bilayer described by Franz, et al., US Patent No. 5,232,704; the multi-layer tablet with a band described by Wong, et al., US Patent No. 6,120,803; the membrane sac and gas generating agent described in Sinnreich, US Patent No. 4,996,058; the swellable, hydrophilic polymer system described in Shell, et al., US

Patent No. 5,972,389 and Shell, et al., WO 9855107; all of which are incorporated herein by reference.

Of particular interest are gastric retained dosage forms that contain hydrophilic polymers that swell to a size such that the dosage form is retained in the fed mode. For example, the gastric retained dosage form can contain polymers with a high swelling capacity such as polyethylene oxide, hydroxyethylcellulose and hydroxypropylmethylcellulose. The polymers are preferably of a moderate to high molecular weight ($4x10^3$ to greater that 10^7) to enhance swelling and provide control of the release of gabapentin. In one embodiment of the invention, a hydroxypropylmethylcellulose polymer of such molecular weight is utilized so that the viscosity of a 1% aqueous solution is about 4000 cps to greater than 100,000 cps. An example of suitable polyethylene oxide polymers are those having molecular weights (viscosity average) on the order of 2-7 million. A typical dosage form should swell to approximately 115% of its original volume within one hour after administration, and at a later time should swell to a volume that is 130% or more of the original volume. Fillers, binders, lubricants and other additives may also be included in the gastric retained dosage form, such as are well known to those of skill in the art.

A typical dosage form would provide for a drug delivery profile such that gabapentin both on an *in vivo* and *in vitro* basis, is delivered for at least 5 hours, and typically over a time period of about 8-10 hours. In order to provide for sustained delivery, it is preferable that at least 40wt% of gabapentin is retained in the dosage form after 1 hour, i.e., no more than 60wt% of the drug is administered in the first hour. In addition, it may be desired to utilize a dosage form that provides for substantially all of the gabapentin to be delivered over the intended duration, which is typically about 6-12 hours, where substantially all is taken to mean at least about 85wt% of the gabapentin is administered.

In one embodiment of the invention, the gastric retained dosage form of gabapentin is a capsule dosage form that allows for the extended release of gabapentin in the stomach and comprises: (a) at least one component that expands on contact with gastric juice and contains an agent capable of releasing carbon dioxide or nitrogen, gabapentin or a pharmaceutically acceptable salt thereof; (b) at least one hydrophilic membrane in the form of a sachet which contains component (a), expands by inflation, floats on the aqueous phase in the stomach and is permeable to gastric juice and; (c) capsule dosage form which

contains components (a) and (b) and which disintegrates without delay in the stomach under the action of gastric juice. Component (a) may also contain a pharmaceutically acceptable hydrophilic swelling agent such as lower alkyl ethers of cellulose, starches, water-soluble aliphatic or cyclic poly-N-vinylamides, polyvinyl alcohols, polyacrylates, polymethacrylates, polyethylene glycols and mixtures thereof, as well as other materials used in the manufacture of pharmaceutical dosage forms. Further details regarding an example of this type of dosage form can be found in Sinnreich, US Patent No. 4,996,058.

In another embodiment of the invention, the gastric retained dosage form of gabapentin is an extended release oral drug dosage form for releasing gabapentin into the stomach, duodenum and small intestine of a patient, and comprises: a single or a plurality of solid particles consisting of gabapentin or a pharmaceutically acceptable salt thereof dispersed within a polymer that (i) swells unrestrained dimensionally by imbibing water from gastric fluid to increase the size of the particles to promote gastric retention in the stomach of the patient in which the fed mode has been induced; (ii) gradually the gabapentin diffuses or the polymer erodes over a time period of hours, where the diffusion or erosion commences upon contact with the gastric fluid; and (iii) releases gabapentin to the stomach, duodenum and small intestine of the patient, as a result of the diffusion or polymeric erosion at a rate corresponding to the time period. Exemplary polymers include polyethylene oxides, alkyl substituted cellulose materials and combinations thereof, for example, high molecular weight polyethylene oxides and high molecular weight or viscosity hydroxypropylmethylcellulose materials. Further details regarding an example of this type of dosage form can be found in Shell, et al., US Patent No. 5,972,389 and Shell, et al., WO 9855107.

In yet another embodiment, a bi-layer tablet releases gabapentin to the upper gastrointestinal tract from an active containing layer, while the other layer is a swelling or floating layer. Details of this dosage may be found in Franz, et al., US Patent No. 5,232,704. This dosage form may be surrounded by a band of insoluble material as described by Wong, et al., US Patent No. 6,120,803.

Another embodiment of the invention uses a gastric retained swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropylmethylcellulose. This dosage form is illustrated in Example 1 and further details may be found in Gusler, et al., "Optimal Polymer Mixtures For Gastric Retentive

Tablets," filed on like date herewith and identified as Attorney Docket No. 15662-001700US, the disclosure of which is incorporated herein by reference.

For those embodiments of the invention that include further administering additional therapeutic agents simultaneously with gabapentin, these agents can either be administered in the gastric retained dosage form that includes gabapentin or can be administered in a dosage form that is separate from gabapentin. Exemplary dosage forms are described below.

Dosage Form of Additional Agents

For those embodiments of the invention that include further administering one or more additional therapeutic agents, such dosages can be any suitable formulation as are well known in the art. For those additional agents where controlled release is desirable, the agent may be incorporated in the gabapentin gastric retained dosage form or be administered in a separate gastric retained or other controlled release formulation dosage form. For those additional agents where immediate release is desirable, the agent may be incorporated in a coating around the gabapentin gastric retained dosage form or in a separate layer of a bilayer tablet, the agent may be simply enclosed in the capsule of the aforementioned gabapentin gastric retained capsule dosage form, or the agent may be administered in a separate immediate release dosage form.

Typically, dosage forms contain the additional agent (another anti-epileptic or anticonvulsant agent) in combination with one or more pharmaceutically acceptable ingredients. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. Usually the amount of active agent is about 0.1-95wt%, more typically about 1-50wt%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 18th Edition, 1990. The dosage form to be administered will, in any event, contain a quantity of the additional therapeutic agent(s) in an amount effective to alleviate the symptoms of the subject being treated.

In the preparation of pharmaceutical formulations containing the additional therapeutic agent in the form of dosage units for oral administration the agent may be mixed with solid, powdered ingredients, such as lactose, microcrystalline cellulose, maltodextrin, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another

suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets such as chewable and oral disintegrating tablets.

Soft gelatin capsules may be prepared by mixing the active agent and vegetable oil, fat, or other suitable vehicle. Hard gelatin capsules may contain granules of the active agent, alone or in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing about 0.2-20wt% of the active agent and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring agents, saccharin and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

When the method of the invention includes administering another anti-epileptic or an anticonvulsant agent, there are numerous commercially available dosage forms that can be administered. In addition, other formulations can be readily designed based upon knowledge in the art, and include the gastric-retained delivery systems described above.

Typical dosage forms of the other anti-epileptics or anticonvulsants suitable for use in the invention include tablets, capsules, oral suspensions and syrup. One of skill in the art can readily prepare one of these exemplary formulations or the other anti-epileptic can be administered by means of one of the numerous commercially available products, examples of which are provided below.

Commercially available hydantoin anticonvulsants include, for example, Peganone® (ethotoin, Abbott); Mesantoin® (mephenytoin, Sandoz); and Dilantin® (phenytoin, Warner-Lambert).

Typical dosage forms of the antineuralgics suitable for use in the invention include tablets, capsules and oral suspensions. One of skill in the art can readily prepare one of these exemplary formulations or the antineuralgic can be administered by means of one of the numerous commercially available products , examples of which are provided below.

Commercially available antineuralgics include, for example, Atretol® (carbamazepine, Elan).

Although specific examples of suitable anti-epileptic, anticonvulsant agent and antineuralgic formulations are described above, it is understood that the invention is not limited to those examples as there are numerous other formulations that can be used to deliver the other anti-epileptic or anticonvulsant agents.

The general methods of the invention are best understood with reference to the following examples which are intended to enable those skilled in the art to more clearly understand and to practice the present invention. These examples are not intended, nor are they to be construed, as limiting the scope of the invention, but are merely illustrative and representative thereof.

Example 1

Tablets were manufactured using a dry blend process, and hand made on a Carver 'Auto C' Press (Fred Carver, Inc., Indiana). The dry blend process consisted of blending all of the ingredients in a plastic bag, and compressing into a 1000 mg tablet (600 mg gabapentin dose) using a 0.7086" x 0.3937" Mod Oval die (Natoli Engineering). The parameters for the operation of the Carver 'Auto C' Press were as follows: 4000 lbs. force, 0 second dwell time (the setting on the Carver Press), and 100% pump speed.

Sample #	Formulation Composition (wt%)			
	Active	PEO Coagulant	Methocel K100M	M. St.
1	60.0	39.0	0.0	1
2	60.0	24.3	14.7	1
3	60.0	0.0	39.0	1

where: Active = gabapentin

PEO Coagulant = poly(ethylene oxide), grade PolyOx Coagulant, NF FP grade, manufactured by Union Carbide/Dow Chemical Company

Methocel K100M = hydroxypropylmethylcellulose, grade Methocel K100M, premium, manufactured by Dow Chemical Company

M.St. = magnesium stearate, NF, supplied by Spectrum Chemical Company

The dissolution was determined in USP apparatus I (40 mesh baskets), 100 rpm, in deionized water. Samples, 5 ml at each time-point, were taken without media replacement at 1, 4 and 8 hours.

The resulting cumulative dissolution profile, based upon a theoretical percent active added to the formulations is presented in tabulated form below:

Time (hours)	Theoretical wt% of Active Released		
	Sample 1	Sample 2	Sample 3
1	15.4	14.8	18.6
4	39.4	37.4	43.3
8	61.7	57.8	64.7

Example 2

Tablets were manufactured using a dry blend process, and hand made on a Carver 'Auto C' Press (Fred Carver, Inc., Indiana). The dry blend process consisted of blending all of the ingredients in a plastic bag, and compressing into a 600 mg tablet (300 mg gabapentin) using a 0.6299" x 0.3937" Mod Oval die (Natoli Engineering). The parameters for the operation of the Carver 'Auto C' Press were as follows: ~2000-2500 lbs. force, 0 second dwell time (the setting on the Carver Press), and 100% pump speed.

Sample #	Formulation Composition (wt%)			
	Active	PEO Coagulant	Methocel K15M	M. St.
4	50.0	24.5	24.50	1

where: Active = gabapentin
PEO Coagulant = poly(ethylene oxide), grade PolyOx Coagulant, NF FP grade, manufactured by Union Carbide/Dow Chemical Company
Methocel K15M = hydroxypropylmethylcellulose, grade Methocel K15M, premium, manufacture by Dow Chemical Company
M.St. = magnesium stearate, NF, supplied by Spectrum Chemical Company

The dissolution was determined in USP apparatus I (40 mesh baskets), 100 rpm, in deionized water. Samples, 5 ml at each time-point, were taken without media replacement at 1, 2, 4 and 8 hours.

The resulting cumulative dissolution profile, based upon a theoretical percent active added to the formulations is presented in tabulated form below:

Time (hours)	Theoretical wt% of Active Released Sample A
1	20.6
2	32.4
4	49.7
6	63.1
8	74.0
10	82.6

Example 3

Three Gastric Retentive (GR™) gabapentin formulas were manufactured utilizing a standard granulation technique. The formulations manufactured are shown in tabulated form below:

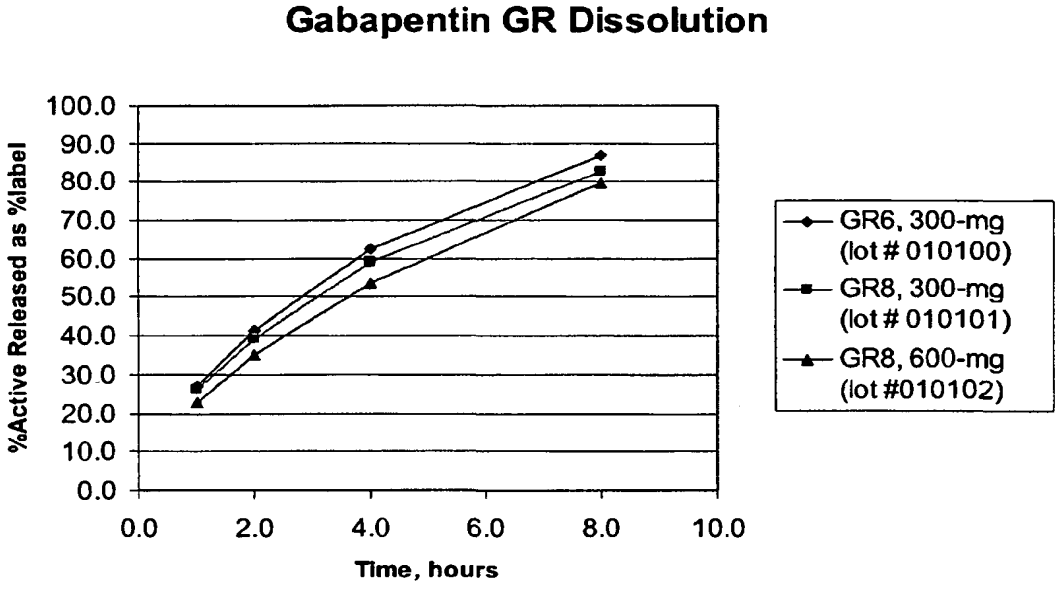
Formulation for Clinical Trial Manufacture		
Gabapentin GR8, 300-mg (GR8, 300-mg)	*Gabapentin GR6, 300-mg (GR6, 300-mg)*	*Gabapentin GR8, 600-mg (GR8, 600-mg)*
44.76% Gabapentin	44.76% Gabapentin	61.11% Gabapentin
21.99% Methocel® K15M, premium	16.46% Methocel® K4M, premium	7.59% Methocel® K15M, premium
21.99% Sentry® PolyOx® WSR Coagulant, NF FP	21.99% Sentry® PolyOx® WSR 303, NF FP	27.09% Sentry® PolyOx® WSR 303, NF FP
7.49% Avicel® PH-101, NF	12.98% Avicel® PH-101, NF	0.00% Avicel® PH-101, NF
2.75% Methocel® E5, prem.	2.75% Methocel® E5, prem.	3.22% Methocel® E5, prem.
1.00% Magnesium Stearate, NF	1.00% Magnesium Stearate, NF	1.00% Magnesium Stearate, NF
670-mg (Tablet weight)	670-mg (Tablet weight)	982-mg (Tablet weight)
0.3937" X 0.6299" Mod Oval	0.3937" X 0.6299" Mod Oval	0.4062" X 0.75" Mod Cap

Gabapentin was obtained from Plantex U.S.A. (Englewood Cliffs, NJ). Methocel® brand hydroxypropyl methylcellulose (also known as hypromellose), and Sentry® PolyOx® brand polyethylene oxide were obtained from Dow Chemical (Midland, Michigan). Methocel E5, premium is a USP type 2910 hydroxypropyl methylcellulose with number average molecular weight of on the order of 6000-8000 and a viscosity of 5 cps as a 2% aqueous solution at 20 °C. Methocel® K4M and Methocel® K15M are USP type 2208 hydroxypropyl methylcellulose with viscosities of 4000 cps and 15,000 cps, respectively, as a 2% aqueous solution at 20 °C, and number average molecular weights on the order of 80,000 and 100,000, respectively. Sentry® PolyOx® WSR 301, NF FP, Sentry® PolyOx® WSR Coagulant, NF FP and Sentry® PolyOx® WSR 303, NF FP have viscosity-average molecular weights of approximately 4,000,000, 5,000,000 and 7,000,000, respectively. Avicel PH-101, NF is microcrystalline cellulose supplied by FMC Corporation

(Philadelphia, PA). Magnesium stearate, NF was supplied by Spectrum Quality Products (New Brunswick, NJ).

The dissolution profiles, as determined by USP Apparatus I (100rpm) in modified simulated gastric fluid, for three prototypes GR™ formulations are shown in Figure 1 below.

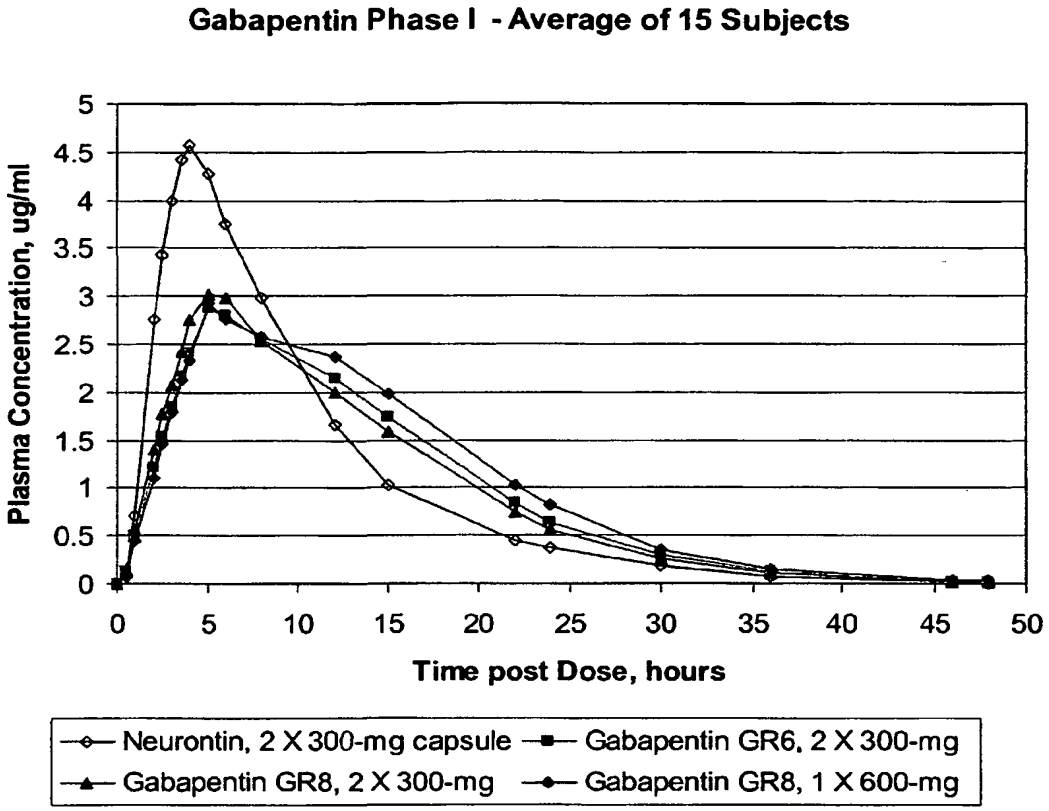
Figure 1



Example 4

The pharmacokinetic profiles of the three formulations described in Example 3, administered as a 600-mg dose, were compared to Neurontin® immediate release 300-mg capsule in a randomized four-way cross-over experiment involving 15 healthy volunteers. Each subject was administered treatment of 600-mg gabapentin as one of the three GR™ formulations (1 X 600-mg tablet or 2 X 300-mg tablet) or Neurontin® capsules (2 X 300-mg) within 5 minutes of completing a high fat breakfast (FDA breakfast). Plasma samples were taken up to 48 hours post-dose. Figure 2 below illustrates the average plasma profile for the four treatments administered, and the pharmacokinetic data are summarized in tabulated form below.

Figure 2



Gabapentin Plasma Data- Average for 15 Subjects				
Dosing		$AUC_{inf}^{\#}$ ((ug/ml)*hr)	$C_{max}^{\#}$ (ug/ml)	T_{max} (hours)
Neurontin®, 300-mg 2 X capsules	Mean:	46.65	4.72	3.93
	%CV:	19.0	20.2	15.1
GR6, 300-mg 2 X tablets	Mean:	44.43	2.97	6.63
	%CV:	34.9	29.7	45.1
GR8, 300-mg 2 X tablets	Mean:	41.84	3.10	5.63
	%CV:	34.4	26.2	34.9
GR8, 600-mg 1 X tablet	Mean:	48.01	3.13	7.13
	%CV:	26.8	18.7	42.2

#Geometric Mean and Geometric %CV are reported here

As demonstrated in Figure 2 and in tabulated form above, GR™ formulations demonstrate sustained release with a lower maximum plasma concentration and a larger value for the time of the maximum concentration compared to the immediate release capsules without loss in the bioavailability as measured by the plasma AUC_{inf}.

Each of the patent applications, patents, publications, and other published documents mentioned or referred to in this specification is herein incorporated by reference in its entirety, to the same extent as if each individual patent application, patent, publication, and other published document was specifically and individually indicated to be incorporated by reference.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

Claims

What is claimed is:

1. A method of treating epilepsy comprising administering a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.

2. The method of Claim 1 wherein the dosage form is administered once-daily.

3. The method of Claim 2 wherein the dosage form is administered with a meal.

4. The method of Claim 1 wherein the dosage form is administered twice-daily.

5. The method of Claim 4 wherein each dosage form is administered with a meal.

6. The method of Claim 1 which further comprises administering one or more additional anti-epileptics or anticonvulsants.

7. The method of Claim 1 wherein the dosage form is administered once- or twice-daily and the total amount of gabapentin in the daily dosage is about 200-4000 mg.

8. The method of Claim 7 wherein the total amount of gabapentin in the daily dosage is about 600-2700 mg.

9. The method of Claim 8 wherein total amount of gabapentin in the daily dosage is about 900-1800 mg.

10. The method of Claim 1 wherein the dosage form is an extended release oral drug dosage form for releasing gabapentin into the stomach, duodenum and small intestine of the mammal.

11. The method of Claim 10 wherein gabapentin is administered from the dosage form for a period of at least 5 hours and at least 40wt% of the gabapentin is retained in the dosage form after 1 hour.

12. The method of Claim 11 wherein the dosage form provides administration of at least 80wt% of the gabapentin to be delivered over a period of about 5-12 hours.

13. The method of Claim 11 wherein the dosage form contains at least one hydrophilic polymer that swells to an extent such that it promotes gastric retention of the dosage form in the fed mode.

14. The method of Claim 13 wherein the polymer is selected from the group consisting of polyethylene oxides, alkyl substituted cellulose materials, and combinations thereof.

15. The method of Claim 11 wherein the dosage form further comprises a gas generating agent.

16. The method of Claim 15 wherein the gabapentin is contained in a membrane sachet with the gas generating agent.

17. The method of Claim 1 wherein the dosage form is an adhesive tablet.

18. The method of Claim 1 wherein the dosage form is a film coated dosage form or a capsule dosage form that allows for the extended release of gabapentin in the stomach duodenum and small intestine of the mammal.

19. The method of Claim 1 wherein the dosage form is a swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropylmethylcellulose.

20. A method of treating neuropathic pain comprising administering a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.

21. The method of Claim 20 wherein the dosage form is administered once-daily.

22. The method of Claim 21 wherein the dosage form is administered with a meal.

23. The method of Claim 20 wherein the dosage form is administered twice-daily.

24. The method of Claim 23 wherein each dosage form is administered with a meal.

25. The method of Claim 20 which further comprises administering one or more therapeutic agents selected from the group consisting of anticonvulsants, tricyclic antidepressants, opioids, and levodopa.

26. The method of Claim 20 wherein the dosage form is administered once- or twice-daily and the total amount of gabapentin in the daily dosage is about 100-4800 mg.

27. The method of Claim 26 wherein the total amount of gabapentin in the daily dosage is about 300-3600 mg.

28. The method of Claim 27 wherein the total amount of gabapentin in the daily dosage is about 900-2400 mg.

29. The method of Claim 20 wherein the dosage form is an extended release oral drug dosage form for releasing gabapentin into the stomach, duodenum and small intestine of the mammal.

30. The method of Claim 29 wherein gabapentin is administered from the dosage form for a period of at least 5 hours and at least 40wt% of the gabapentin is retained in the dosage form after 1 hour.

31. The method of Claim 30 wherein the dosage form provides administration of at least 85wt% of the gabapentin to be delivered over a period of about 5-12 hours.

32. The method of Claim 30 wherein the dosage form contains at least one hydrophilic polymer that swells to an extent such that it promotes gastric retention of the dosage form in the fed mode.

33. The method of Claim 32 wherein the polymer is selected from the group consisting of polyethylene oxides, alkyl substituted cellulose materials, and combinations thereof.

34. The method of Claim 30 wherein the dosage form further comprises a gas generating agent.

35. The method of Claim 34 wherein the gabapentin is contained in a membrane sachet with the gas generating agent.

36. The method of Claim 20 wherein the dosage form is an adhesive tablet.

37. The method of Claim 20 wherein the dosage form is a film coated dosage form or a capsule dosage form that allows for the extended release of gabapentin in the stomach duodenum and small intestine of the mammal.

38. The method of Claim 20 wherein the dosage form is a swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropylmethylcellulose.

39. A method of treating psychiatric disorders comprising administering a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.

40. The method of Claim 39 wherein the psychiatric disorder is bipolar disorder or panic disorder.

41. The method of Claim 39 wherein the dosage form is administered once-daily.

42. The method of Claim 41 wherein the dosage form is administered with a meal.

43. The method of Claim 39 wherein the dosage form is administered twice-daily.

44. The method of Claim 43 wherein each dosage form is administered with a meal.

45. The method of Claim 39 which further comprises administering one or more therapeutic agents selected from the group consisting of anticonvulsants, tricyclic antidepressants, opioids, and levodopa.

46. The method of Claim 39 wherein the dosage form is administered once- or twice-daily and the total amount of gabapentin in the daily dosage is about 100-4800 mg.

47. The method of Claim 46 wherein the total amount of gabapentin in the daily dosage is about 900-3600 mg.

48. The method of Claim 39 wherein the dosage form is an extended release oral drug dosage form for releasing gabapentin into the stomach, duodenum and small intestine of the mammal.

49. The method of Claim 48 wherein gabapentin is administered from the dosage form for a period of at least 5 hours and at least 40wt% of the gabapentin is retained in the dosage form after 1 hour.

50. The method of Claim 49 wherein the dosage form provides administration of at least 85wt% of the gabapentin to be delivered over a period of about 5-12 hours.

51. The method of Claim 49 wherein the dosage form contains at least one hydrophilic polymer that swells to an extent such that it promotes gastric retention of the dosage form in the fed mode.

52. The method of Claim 51 wherein the polymer is selected from the group consisting of polyethylene oxides, alkyl substituted cellulose materials, and combinations thereof.

53. The method of Claim 49 wherein the dosage form further comprises a gas generating agent.

54. The method of Claim 53 wherein the gabapentin is contained in a membrane sachet with the gas generating agent.

55. The method of Claim 39 wherein the dosage form is an adhesive tablet.

56. The method of Claim 39 wherein the dosage form is a film coated dosage form or a capsule dosage form that allows for the extended release of gabapentin in the stomach.

57. The method of Claim 39 wherein the dosage form is a swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropylmethylcellulose.

58. A method of treating movement disorders comprising administering a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.

59. The method of Claim 58 wherein the movement disorder is restless leg syndrome, periodic movement disorder of sleep, essential tremor or acquired nystagmus.

60. The method of Claim 58 wherein the dosage form is administered once-daily.

61. The method of Claim 60 wherein the dosage form is administered with a meal.

62. The method of Claim 58 wherein the dosage form is administered twice-daily.

63. The method of Claim 62 wherein each dosage form is administered with a meal.

64. The method of Claim 58 which further comprises administering one or more therapeutic agents selected from the group consisting of anticonvulsants, tricyclic antidepressants, opioids, benzodiazepine, and dopaminergic agents.

65. The method of Claim 58 wherein the dosage form is administered once- or twice-daily and the total amount of gabapentin in the daily dosage is about 100-4000 mg.

66. The method of Claim 65 wherein the total amount of gabapentin in the daily dosage is about 200-3000 mg.

67. The method of Claim 66 wherein the total amount of gabapentin in the daily dosage is about 500-2700 mg.

68. The method of Claim 58 wherein the dosage form is an extended release oral drug dosage form for releasing gabapentin into the stomach, duodenum and small intestine of the mammal.

69. The method of Claim 68 wherein gabapentin is administered from the dosage form for a period of at least 5 hours and at least 40wt% of the gabapentin is retained in the dosage form after 1 hour.

70. The method of Claim 69 wherein the dosage form provides administration of at least 80wt% of the gabapentin to be delivered over a period of about 5-12 hours.

71. The method of Claim 69 wherein the dosage form contains a hydrophilic polymer that swells to a size such that the dosage form is retained in the fed mode.

72. The method of Claim 71 wherein the polymer is selected from the group consisting of polyethylene oxides, alkyl substituted cellulose materials, and combinations thereof.

73. The method of Claim 69 wherein the dosage form further comprises a gas generating agent.

74. The method of Claim 73 wherein the gabapentin is contained in a membrane sachet with the gas generating agent.

75. The method of Claim 58 wherein the dosage form is an adhesive tablet.

76. The method of Claim 58 wherein the dosage form is a film coated dosage form or a capsule dosage form that allows for the extended release of gabapentin in the stomach.

77. The method of Claim 58 wherein the dosage form is a swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropylmethylcellulose.

78. A method for the prophylactic treatment of migraine headaches comprising administering a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.

79. The method of Claim 78 wherein the dosage form is administered once-daily.

80. The method of Claim 79 wherein the dosage form is administered with a meal.

81. The method of Claim 78 wherein the dosage form is administered twice-daily.

82. The method of Claim 81 wherein each dosage form is administered with a meal.

83. The method of Claim 78 which further comprises administering one or more therapeutic agents selected from the group consisting of anticonvulsants, tricyclic antidepressants, opioids, and levodopa.

84. The method of Claim 78 wherein the dosage form is administered once- or twice-daily and the total amount of gabapentin in the daily dosage is about 200-4000 mg.

85. The method of Claim 84 wherein the total amount of gabapentin in the daily dosage is about 500-3600 mg.

86. The method of Claim 85 wherein the total amount of gabapentin in the daily dosage is about 900-2400 mg.

87. The method of Claim 78 wherein the dosage form is an extended release oral drug dosage form for releasing gabapentin into the stomach, duodenum and small intestine of the mammal.

88. The method of Claim 87 wherein gabapentin is administered from the dosage form for a period of at least 5 hours and at least 40wt% of the gabapentin is retained in the dosage form after 1 hour.

89. The method of Claim 88 wherein the dosage form provides administration of at least 85wt% of the gabapentin to be delivered over a period of about 5-12 hours.

90. The method of Claim 88 wherein the dosage form contains at least one hydrophilic polymer that swells to an extent such that it promotes gastric retention of the dosage form in the fed mode.

91. The method of Claim 90 wherein the polymer is selected from the group consisting of polyethylene oxides, alkyl substituted cellulose materials, and combinations thereof.

92. The method of Claim 88 wherein the dosage form further comprises a gas generating agent.

93. The method of Claim 92 wherein the gabapentin is contained in a membrane sachet with the gas generating agent.

94. The method of Claim 78 wherein the dosage form is an adhesive tablet.

95. The method of Claim 78 wherein the dosage form is a film coated dosage form or a capsule dosage form that allows for the extended release of gabapentin in the stomach duodenum and small intestine of the mammal.

96. The method of Claim 78 wherein the dosage form is a swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropylmethylcellulose.

97. An improved method of administering a therapeutically effective amount of gabapentin to a patient in need thereof, the improvement comprising administering gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form.

98. The method of Claim 97 wherein the dosage form is administered once-daily.

99. The method of Claim 98 wherein the dosage form is administered with a meal.

100. The method of Claim 97 wherein the dosage form is administered twice-daily.

101. The method of Claim 100 wherein each dosage form is administered with a meal.

102. The method of Claim 97 where the patient is being treated for epilepsy.

103. The method of Claim 97 where the patient is being treated for neuropathic pain.

104. The method of Claim 97 where the patient is being treated for psychiatric disorders.

105. The method of Claim 97 where the patient is being treated for movement disorders.

106. The method of Claim 97 where the patient is receiving prophylactic treatment for migraine headaches.

107. The method of Claim 97 wherein the dosage form is an extended release oral drug dosage form for releasing gabapentin into the stomach, duodenum and small intestine of the mammal.

108. The method of Claim 107 wherein gabapentin is administered from the dosage form for a period of at least 5 hours and at least 40wt% of the gabapentin is retained in the dosage form after 1 hour.

109. The method of Claim 108 wherein the dosage form provides administration of at least 80wt% of the gabapentin to be delivered over a period of about 5-12 hours.

110. The method of Claim 108 wherein the dosage form contains at least one hydrophilic polymer that swells to an extent such that it promotes gastric retention of the dosage form in the fed mode.

111. The method of Claim 110 wherein the polymer is selected from the group consisting of polyethylene oxides, alkyl substituted cellulose materials, and combinations thereof.

112. The method of Claim 108 wherein the dosage form further comprises a gas generating agent.

113. The method of Claim 112 wherein the gabapentin is contained in a membrane sachet with the gas generating agent.

114. The method of Claim 97 wherein the dosage form is an adhesive tablet.

115. The method of Claim 97 wherein the dosage form is a film coated dosage form or a capsule dosage form that allows for the extended release of gabapentin in the stomach.

116. The method of Claim 97 wherein the dosage form is a swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropyl methylcellulose.

INTERNATIONAL SEARCH REPORT

Interna | Application No
PCT, .. 02/05440

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 03 002151 A (MASSIRONI MARIA GABRIELLA ;FARMATRON LTD (GB)) 9 January 2003 (2003-01-09) page 12 -page 13; example 4 page 9, line 9 - line 11 ---	1-5, 7-14,18, 97-102, 107-111, 115
A	MAGNUS L: "NONEPILEPTIC USES OF GABAPENTIN" EPILEPSIA, RAVEN PRESS LTD., NEW YORK, US, vol. 40, no. SUPPL 6, 1999, pages S66-S72, XP000866519 ISSN: 0013-9580 the whole document --- -/--	1-116

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 March 2003	14/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muller, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/IB 02/05440

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 906 832 A (KUCZYNSKI ANTHONY L ET AL) 25 May 1999 (1999-05-25) column 2, line 61 - line 63 column 9, line 10 - line 67 column 17; example 13 claim 1	1-14, 18-33, 37-52, 56-72, 76-91, 95-111, 115,116
X	EP 1 118 321 A (UCB SA) 25 July 2001 (2001-07-25) page 3, line 30 - line 45 page 6 -page 7; example 1 claims 1,2	1-5, 7-14, 20-24, 26-33, 39-44, 46-52, 58-63, 65-72, 78-82, 84-91, 97-111
A	WO 01 13894 A (PUREPAC PHARMACEUTICAL CO) 1 March 2001 (2001-03-01) page 14; table 1	1-116

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int onal application No.
rCT/IB 02/05440

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-116 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/IB 02/05440

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 03002151	A	09-01-2003	WO	03002151 A1	09-01-2003
US 5906832	A	25-05-1999	AU	693546 B2	02-07-1998
			AU	2291295 A	29-11-1995
			CA	2184395 A1	09-11-1995
			EP	0758228 A1	19-02-1997
			JP	9512550 T	16-12-1997
			NZ	284326 A	24-04-1997
			WO	9529665 A1	09-11-1995
			US	5660861 A	26-08-1997
			US	5876750 A	02-03-1999
			US	5955103 A	21-09-1999
			US	5863558 A	26-01-1999
			ZA	9503078 A	05-01-1996
EP 1118321	A	25-07-2001	EP	1118321 A1	25-07-2001
			AU	2169501 A	24-07-2001
			WO	0151033 A1	19-07-2001
WO 0113894	A	01-03-2001	US	6294198 B1	25-09-2001
			AU	6925400 A	19-03-2001
			WO	0113894 A1	01-03-2001
			US	2003008004 A1	09-01-2003
			US	2001043946 A1	22-11-2001